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# Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study

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## Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study.

**Background.** Cardiovascular mortality is extremely high in end-stage renal disease. Cardiovascular mortality risk also is increased in selected (high-risk) individuals with mild to moderate impairment of renal function. It is not clear whether a similar association exists in the general population and, if so, through what mechanisms. We investigated the association of renal function with all-cause and cardiovascular mortality in a population-based cohort and explored potential mechanisms underlying any such relationship.

**Methods.** An age-, sex-, and glucose-tolerance-stratified sample ( $N = 631$ ) of a population-based cohort aged 50 to 75 years was followed prospectively. After up to 10.2 years of follow-up, 117 subjects had died (50 of cardiovascular causes). At baseline, renal function was estimated by the serum creatinine level, the Cockcroft-Gault formula and Levey's equation.

**Results.** At baseline, the mean age was  $64 \pm 7$  years, 48% were men, 55% had hypertension, and 27% (by design) had type 2 diabetes. Serum creatinine was  $91.7 \pm 19.0$   $\mu\text{mol/L}$ ; creatinine clearance as estimated by the Cockcroft-Gault formula was  $72.5 \pm 13.7$   $\text{mL/min/1.73 m}^2$ , and the glomerular filtration rate (GFR) estimated by Levey's equation was  $67.8 \pm 12.1$   $\text{mL/min/1.73 m}^2$ . Renal function was inversely associated with all-cause and with cardiovascular mortality. Relative risks (95% confidence intervals) were 1.08 (1.04 to 1.13) and 1.11 (1.07 to 1.16) per 5  $\mu\text{mol/L}$  increase of serum creatinine; 1.07 (0.98 to 1.17) and 1.15 (1.01 to 1.31) for each decrease of 5  $\text{mL/min/1.73 m}^2$  creatinine clearance; and 1.15 (1.05 to 1.26) and 1.26 (1.12 to 1.42) for each decrease of 5  $\text{mL/min/1.73 m}^2$  of GFR. These associations remained after adjusting for age, sex, glucose tolerance status, hypertension, prior cardiovascular disease, low-density lipoprotein cholesterol, homocysteine, (micro)albuminuria, von Willebrand factor, soluble vascular adhesion molecule-1 and C-reactive protein. Analyses in diabetic and hypertensive subjects gave similar results.

**Conclusion.** Mild to moderate loss of renal function is strongly associated with an increased risk of cardiovascular mortality.

**Key words:** renal function, mortality, general population, risk factors, atherosclerosis, glomerular filtration rate.

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The mechanism behind this association is unclear but does not appear to involve common risk factors such as hypertension, diabetes or hyperhomocysteinemia. Estimation of renal function by relatively simple methods therefore may be a valuable tool for cardiovascular risk assessment over and above that provided by conventional risk factors. Our results were obtained in a general middle-aged to elderly population, and thus have broad applicability.

End-stage renal disease is strongly associated with risk of cardiovascular disease [1]. It is not clear whether a similar association exists for patients with less severely impaired renal function [2, 3], nor by which mechanisms any such association would be mediated. This question is important because the incidence of renal functional impairment is increasing rapidly [4].

Estimation of glomerular filtration rate by gold-standard clearance methods using exogenous tracers is unsuitable for large-scale studies. Population-based studies therefore require simpler estimates of renal function, such as the serum creatinine level [5], the Cockcroft-Gault formula [6] or Levey's prediction equation, which may be most accurate [7]. However, it is not known whether these estimates of renal function differ in their association with cardiovascular disease.

In view of these considerations, in a prospective, population-based study, we investigated whether these estimates of renal function were associated with cardiovascular mortality. In addition, we explored potential mechanisms to explain any such relationship, such as increased blood pressure, hyperhomocysteinemia, endothelial dysfunction and inflammatory activity, all of which are associated with both impaired renal function and cardiovascular disease [4, 8].

## METHODS

### General study design

The study population consisted of a sample of the Hoorn Study, which for reasons of efficiency was strati-

fied for age, sex, and glucose tolerance. The Hoorn Study is a population-based cohort study of glucose tolerance and other cardiovascular risk factors in a Caucasian population aged 50 to 75 years, in which the baseline measurements were conducted from 1989 to 1992, as described previously [9, 10].

The present study population thus represents a stratified random sample of all subjects in the initial Hoorn Study cohort.

### Baseline investigations

Renal function was estimated by three calculations: the serum creatinine level in  $\mu\text{mol/L}$  [11]; the Cockcroft-Gault formula in  $\text{mL/min}$   $[(140 - \text{age}) * \text{body weight} / (\text{creatinine} * 72) * 0.85 \text{ if female}]$  [6]; and Levey's prediction equation in  $\text{mL/min}$   $[170 * (\text{creatinine})^{-0.999} * (\text{age})^{-0.176} * (\text{urea})^{-0.170} * (\text{albumin})^{+0.318} * 0.762 \text{ if female}]$  [7]. The Cockcroft-Gault and Levey's formulas were both expressed per  $1.73 \text{ m}^2$  body surface area [12]. (Formulas are given in traditional units. To convert to International System units multiply creatinine in  $\text{mg/dL}$  by 88.4, urea in  $\text{mg/dL}$  by 0.357 and albumin in  $\text{g/dL}$  by 10.)

### Other measurements

Data were obtained on smoking habits, blood pressure, weight, height, body mass index, waist-to-hip ratio, and ankle-brachial pressure index, as described elsewhere [9, 10]. The following criteria were measured: serum levels of fasting glucose, two-hour post-load glucose, glycated hemoglobin, fasting insulin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, homocysteine, von Willebrand factor, soluble vascular cell adhesion molecule-1 (sVCAM-1), and C-reactive protein [9, 10, 13]. Resting electrocardiograms were made and classified according to the Minnesota coding system [14]. Hypertension was defined as a blood pressure  $\geq 140 \text{ mm Hg}$  systolic and/or  $\geq 90 \text{ mm Hg}$  diastolic, according to JNC VI criteria [15] and/or the current use of antihypertensive medication. Pulse pressure was calculated by subtracting the mean diastolic blood pressure from the mean systolic blood pressure. (Micro)albuminuria was defined as an albumin-to-creatinine ratio  $> 2.0 \text{ mg/mmol}$  [10]. Subjects were classified as having cardiovascular disease if they had a history of myocardial infarction, an electrocardiogram with a Minnesota code 1.1–1.3, 4.1–4.3, 5.1–5.3 or 7.1, had undergone coronary bypass surgery or angioplasty, had an ankle-brachial pressure index less than 0.9 in either leg, and/or had undergone a peripheral arterial bypass or amputation for atherosclerotic disease.

### Follow-up

Data on the subjects' vital status on January 1, 2000 were collected from the mortality register of the municipality of Hoorn. Of 51 subjects who had moved out of

town, information on vital status was obtained from the new local municipalities. For each subject, we determined whether or not death had occurred during follow-up, and if so, the date when death occurred. For all subjects who died, the cause of death was extracted from the medical records of the general practitioner and the hospital of Hoorn, and classified according to the ninth edition of the *International Classification of Diseases* [16]. Cardiovascular mortality was defined as codes 390–459. Information on cause of death could not be obtained for 16 (15%) of the deceased subjects and one subject was lost to follow-up. The Hoorn Study was approved by the Ethical Review Committee of the VU University Medical Centre. Written informed consent was obtained from all participants.

### Statistical analyses

All analyses were performed using the SPSS 10.1 software program for Windows 98 (SPSS, Chicago, IL, USA). The Cox proportional hazard analyses were used to assess the associations with all-cause and cardiovascular mortality of estimates of renal function and of cardiovascular risk factors, such as hypertension, and risk indicators, such as von Willebrand factor, in all cases—because of the stratification procedure—with an adjustment for age, sex and glucose tolerance status. Risk factors and indicators measured on a continuous scale were used as such in the regression models, except for body mass index and waist-to-hip ratio, and levels of high-density lipoprotein cholesterol, von Willebrand factor and C-reactive protein, because the association of these variables with mortality appeared to be non-linear. Therefore, obesity was defined as a body mass index above  $27 \text{ kg/m}^2$  for men and above  $26 \text{ kg/m}^2$  for women [17]; a high waist-to-hip ratio as above 0.95 for men and above 0.80 for women [18]; a low level of high-density lipoprotein cholesterol as below  $0.9 \text{ mmol/L}$  [19]; and a high level of von Willebrand factor or C-reactive protein as a level in the upper tertile ( $> 1.56 \text{ IU/mL}$  and  $> 2.84 \text{ mg/L}$ , respectively) [20]. Levels of fasting insulin, triglyceride and sVCAM-1 were log-transformed because of a better fit of the regression model.

Multivariate Cox proportional hazard analyses were performed to assess whether the associations of estimates of renal function with all-cause and cardiovascular mortality were independent of potential confounders. Results are described as relative risks (hazard ratios) with 95% confidence intervals. Diabetes and hypertension are often accompanied by impaired renal function. Interaction terms were used to investigate whether the association between estimates of renal function and mortality differed according to blood pressure status or presence of diabetes, because any such interaction might be clinically important. Two-sided *P* values less than 0.05 were considered statistically significant.

**Table 1.** Population characteristics and relative risk of all-cause and cardiovascular mortality associated with risk factors or risk indicators

Risk factor or indicator	All subjects ( <i>N</i> = 631) percentage, mean $\pm$ SD, median (iqr)	Difference in risk factor or indicator	All-cause mortality	Cardiovascular mortality
			Relative risk (95%CI)	
Male gender	48%	yes vs. no	1.56 (1.08–2.26)	1.14 (0.81–2.48)
Age	64 $\pm$ 7 years	per 5 year increase	1.60 (1.38–1.86)	1.59 (1.26–1.86)
Diabetes mellitus type 2	27%	yes vs. no	2.38 (1.65–3.43)	3.02 (1.73–5.28)
Glycated hemoglobin	5.9 $\pm$ 1.3%	per 1% increase of hemoglobin	1.14 (1.00–1.30)	1.10 (0.91–1.34)
Fasting insulin	84 (63–119) pmol/L	per 10% increase <sup>a</sup>	1.03 (1.01–1.07)	1.02 (0.96–1.09)
Body mass index	27.2 $\pm$ 4.0 kg/m <sup>2</sup>	high vs. low <sup>b</sup>	1.36 (0.91–2.04)	1.92 (1.00–3.69)
Waist-to-hip ratio	0.92 $\pm$ 0.09	high vs. low	2.01 (1.17–3.49)	1.84 (0.80–4.23)
Total cholesterol	6.6 $\pm$ 1.2 mmol/L	per 1.0 mmol/L increase	1.11 (0.96–1.29)	1.14 (0.91–1.42)
High-density lipoprotein cholesterol	1.3 $\pm$ 0.4 mmol/L	high vs. low <sup>c</sup>	1.85 (1.16–2.96)	2.67 (1.37–5.18)
Low-density lipoprotein cholesterol	4.5 $\pm$ 1.1 mmol/L	per 1.0 mmol/L increase	1.08 (0.92–1.28)	1.14 (0.89–1.46)
Triglycerides	1.6 (1.2–2.2) mmol/L	per 10% increase <sup>a</sup>	1.05 (1.01–1.09)	1.05 (0.99–1.11)
Hypertension	55%	yes vs. no	2.65 (1.74–4.04)	4.03 (1.96–8.30)
Systolic blood pressure	139 $\pm$ 19 mm Hg	per 10 mm Hg increase	1.08 (0.98–1.19)	1.15 (0.99–1.33)
Diastolic blood pressure	83 $\pm$ 10 mm Hg	per 10 mm Hg increase	1.03 (0.86–1.23)	1.05 (0.80–1.39)
Pulse pressure	57 $\pm$ 15 mm Hg	per 10 mm Hg increase	1.14 (1.00–1.29)	1.24 (1.02–1.51)
Prior cardiovascular disease	24%	yes vs. no <sup>f</sup>	2.13 (1.46–3.10)	2.82 (1.59–5.02)
Current smoking	28%	yes vs. no	1.68 (1.13–2.49)	1.60 (0.86–2.99)
Homocysteine	12.6 $\pm$ 5.8 $\mu$ mol/L	per 5 $\mu$ mol/L increase	1.08 (0.96–1.21)	1.10 (0.95–1.28)
C-reactive protein	1.75 (0.83–3.80) mg/L	high vs. low <sup>d</sup>	1.42 (0.97–2.07)	1.80 (1.01–3.19)
von Willebrand factor	1.37 $\pm$ 0.69 IU/mL	high vs. low <sup>d</sup>	1.76 (1.20–2.56)	2.08 (1.17–3.71)
sVCAM-1	1304.8 (1098.8–1594.6) $\mu$ g/L	per 10% increase <sup>a</sup>	1.04 (0.98–1.11)	1.14 (1.04–1.26)
Albumin	38.7 $\pm$ 2.8 g/L	per 1 g/L decrease	1.10 (1.10–1.18)	1.19 (1.08–1.32)
(Micro)albuminuria	11%	yes vs. no	1.76 (1.12–2.78)	3.02 (1.63–5.60)
GFR				
Serum creatinine level	91.7 $\pm$ 19.0 $\mu$ mol/L (80–100)	per 5 $\mu$ mol/L increase	1.08 (1.05–1.12)	1.11 (1.07–1.16)
Cockcroft-Gault formula	72.5 $\pm$ 13.7 mL/min (63.3–81.2)	per 5 mL/min decrease	1.04 (0.97–1.11)	1.15 (1.01–1.31)
Levey's equation	67.8 $\pm$ 12.1 mL/min (59.7–75.5)	per 5 mL/min decrease	1.15 (1.05–1.26)	1.26 (1.12–1.42)

Relative risks with 95% confidence intervals (95%CI) obtained with Cox proportional hazard analyses after adjustment for age, sex and glucose-tolerance-status, except when this was the variable under consideration. Creatinine clearance, estimated by the Cockcroft-Gault formula, and the glomerular filtration rate, estimated by Levey's equation, were both expressed per 1.73 m<sup>2</sup> \*log-transformed; <sup>b</sup> > vs.  $\leq$  27 kg/m<sup>2</sup> for males and > vs.  $\leq$  26 kg/m<sup>2</sup> for females; <sup>c</sup> < vs.  $\geq$  0.9 mmol/L; <sup>d</sup> upper tertile vs. lower tertile (>1.56 IU/mL for von Willebrand factor and >2.84 mg/L for C-reactive protein levels); <sup>e</sup> albumin-to-creatinine ratio vs.  $\geq$  2.0 mg/mmol; <sup>f</sup> See **Methods**. Abbreviations are: sVCAM-1, soluble vascular cell adhesion molecule-1; SD, standard deviation; iqr, interquartile range.

## RESULTS

### Follow-up duration

Median duration of the follow-up was 8.74 (range 0.46 to 10.19) years. During follow-up, 117 of 631 subjects died, 50 (43%) of cardiovascular disease.

### Clinical characteristics

Table 1 shows the baseline characteristics of the study population. The serum creatinine level was 91.7  $\pm$  19.0 ( $\pm$  SD)  $\mu$ mol/L. Mean creatinine clearance, as estimated by the Cockcroft-Gault formula, was 72.5  $\pm$  13.7 ( $\pm$  SD) mL/min/1.73 m<sup>2</sup>, and mean glomerular filtration rate (GFR), as estimated by Levey's prediction equation, was 67.8  $\pm$  12.1 ( $\pm$  SD) mL/min/1.73 m<sup>2</sup>. Table 1 also shows the relative risks of mortality associated with risk factors and risk indicators. The relative risks for the estimates of renal function are expressed per a 5 unit increase for creatinine and a 5 unit decrease for the other estimates.

### Estimates of renal function and all-cause and cardiovascular mortality

All estimates of renal function were associated with both all-cause and cardiovascular mortality, so that an impaired renal function was accompanied by a higher mortality risk (Tables 2 and 3). The highest relative risk was seen for Levey's equation (model 1; Fig. 1). If expressed per 1 SD change in the renal function estimate, the relative risks of cardiovascular disease in model 1 were 1.49 (95% confidence interval, 1.28 to 1.73) for serum creatinine, 1.47 (1.04 to 2.08) for the Cockcroft-Gault formula, and 1.77 (1.33 to 2.34) for Levey's equation. Adjustment for potential confounders did not materially change the relative risks (models 2 to 8). Adding body mass index or waist-to-hip ratio, or replacing hypertension by systolic, diastolic or pulse pressure did not influence the associations either (data not shown). These results did not differ according to the blood pressure level, or the presence of hypertension or diabetes (*P* values for interaction >0.10).

**Table 2.** Relative risks of all-cause mortality associated with the different estimates of renal function

All-cause mortality ( <i>N</i> = 117)		All subjects ( <i>N</i> = 608) <sup>a</sup> relative risk (95%CI)		
Model	Added variables	Serum creatinine level	Cockcroft-Gault formula	Levey's equation
1.	Age, sex, glucose tolerance status	1.08 (1.04–1.13)	1.07 (0.98–1.17)	1.15 (1.05–1.26)
2.	Model 1 + prior CVD + hypertension	1.07 (1.03–1.11)	1.07 (0.98–1.17)	1.12 (1.04–1.21)
3.	Model 2 + LDL cholesterol	1.07 (1.03–1.11)	1.06 (0.97–1.16)	1.12 (1.04–1.21)
4.	Model 2 + homocysteine	1.07 (1.03–1.11)	1.07 (0.98–1.17)	1.12 (1.03–1.23)
5.	Model 2 + (micro)albuminuria	1.07 (1.03–1.11)	1.07 (0.98–1.17)	1.11 (1.02–1.21)
6.	Model 2 + von Willebrand factor	1.06 (1.02–1.10)	1.08 (0.99–1.18)	1.12 (1.04–1.21)
7.	Model 2 + sVCAM-1	1.07 (1.03–1.11)	1.08 (0.99–1.18)	1.13 (1.04–1.22)
8.	Model 2 + C-reactive protein	1.08 (1.03–1.11)	1.08 (0.99–1.18)	1.13 (1.04–1.22)

Variables are defined in the legend to Table 1. Abbreviations are: CVD, cardiovascular disease; sVCAM-1, soluble vascular cell adhesion molecule-1.

<sup>a</sup>Complete data were available in 608 individuals

**Table 3.** Relative risks of cardiovascular mortality associated with the different estimates of renal function

Cardiovascular mortality ( <i>N</i> = 50)		All subjects ( <i>N</i> = 608) relative risk (95%CI)		
Model	Added variables	Serum creatinine level	Cockcroft-Gault formula	Levey's equation
1.	Age, sex, glucose tolerance status	1.11 (1.07–1.16)	1.15 (1.01–1.31)	1.26 (1.12–1.42)
2.	Model 1 + prior CVD + hypertension	1.09 (1.05–1.13)	1.14 (1.01–1.28)	1.22 (1.09–1.35)
3.	Model 2 + LDL cholesterol	1.09 (1.05–1.13)	1.14 (1.01–1.28)	1.22 (1.09–1.35)
4.	Model 2 + homocysteine	1.09 (1.04–1.15)	1.14 (1.01–1.30)	1.22 (1.08–1.37)
5.	Model 2 + (micro)albuminuria	1.08 (1.04–1.13)	1.13 (1.00–1.27)	1.19 (1.05–1.33)
6.	Model 2 + von Willebrand factor	1.08 (1.04–1.13)	1.14 (1.01–1.28)	1.20 (1.07–1.33)
7.	Model 2 + sVCAM-1	1.09 (1.05–1.13)	1.14 (1.01–1.28)	1.19 (1.06–1.34)
8.	Model 2 + C-reactive protein	1.09 (1.05–1.14)	1.14 (1.02–1.29)	1.21 (1.08–1.36)

Variables are defined in the legend to Table 1. Abbreviations are: CVD, cardiovascular disease; sVCAM-1, soluble vascular cell adhesion molecule-1.

## Additional analyses

As age and sex were part of the Cockcroft-Gault formula and Levey's equation, and were added to the analyses with serum creatinine as key independent variable, all models were tested without these (stratification) variables. This did not materially influence our results. For example, the cardiovascular mortality risks, without age and sex, for creatinine, creatinine clearance and glomerular filtration rate were 1.10 (1.06–1.14), 1.16 (1.07–1.26) and 1.29 (1.16–1.44), respectively (other data not shown).

Further analyses to exclude the effects of modification by the presence of hypertension or diabetes confirmed the consistency of the results, as the association between renal function and cardiovascular mortality was similar regardless of the presence or absence of hypertension or diabetes (data not shown).

Results were similar when subjects with GFR <30 mL/min/1.73 m<sup>2</sup> according to Levey's equation (*N* = 4) were excluded from the analyses.

No violations of the Cox's proportional hazard assumption were observed.

## DISCUSSION

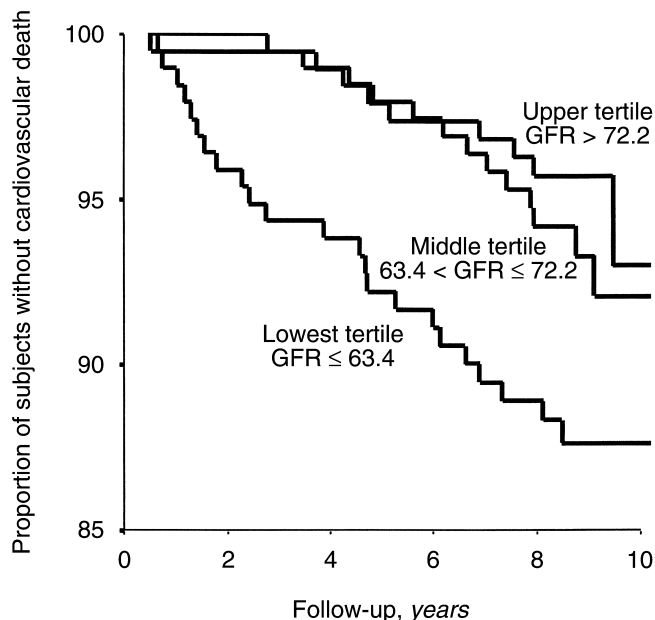
This population-based study shows that relatively small impairments of renal function are associated with increased risk of cardiovascular mortality, regardless of whether renal function was estimated by the serum creatinine level, the Cockcroft-Gault formula or Levey's prediction equation.

According to Levey's equation, glomerular filtration rate varied between 16.8 and 116.9 mL/min/1.73 m<sup>2</sup>. Within this range, a decrease in glomerular filtration rate of 5 mL/min/1.73 m<sup>2</sup> was associated with a 26% increase in risk of cardiovascular death. Thus, a decrease from 90 to 60 mL/min/1.73 m<sup>2</sup> was associated with fourfold (that is, 1.26<sup>6</sup>) increase in risk of cardiovascular death. Surprisingly, the association between mild renal insufficiency and cardiovascular mortality could not be explained by the presence of hypertension, diabetes or prior cardiovascular disease, the lipid profile, the homocysteine level, or by markers of endothelial dysfunction or inflammation. The mechanism responsible for the association thus remains unclear.

Our data are consistent with results of most, but not all [21], previous studies on the association between minor renal impairment and cardiovascular disease that have targeted selected populations, such as pre-dialysis patients [22], patients with a recent stroke [23] or a myocardial infarction [24], patients at high risk of cardiovascular disease [25], patients with hypertension [26–28] and middle-aged men [29].

Population-based studies, however, are scarce and have shown discordant results [2, 3, 30]. In the Cardiovascular Health Study, serum creatinine levels greater than 133 μmol/L were associated with a 71% increase in risk of all-cause mortality [30]. However, the Framingham





**Fig. 1.** Cardiovascular survival (Kaplan-Meier) according to tertiles of glomerular filtration rate (GFR), estimated by Levey's equation and expressed per mL/min/1.73 m<sup>2</sup>.

Study showed that serum creatinine levels between 136 and 265  $\mu\text{mol/L}$  for men and between 120 and 265  $\mu\text{mol/L}$  for women were associated with all-cause mortality in men, but not in women. In addition, associations with cardiovascular mortality were not significant in either sex after adjustment for conventional cardiovascular risk factors (that is, diabetes, hypertension and prevalent cardiovascular disease) [2]. Finally, results from the NHANES I study showed that moderate renal insufficiency, defined as a creatinine of 104 to 146  $\mu\text{mol/L}$  for women and 122 to 177  $\mu\text{mol/L}$  in men, was significantly associated with both all-cause and cardiovascular mortality, but both associations lost significance after adjustment for traditional cardiovascular risk factors [3]. These different results may be related to the fact that the mortality rate in these studies [2, 3, 30] was lower than in our study. In addition, the NHANES I study used a narrower definition of renal insufficiency than our current study.

Levey's equation may provide a more accurate method to estimate renal function than the Cockcroft-Gault formula [7]. Our data support this concept in that Levey's equation showed the strongest association with mortality (because the most accurate estimate of renal function would be expected to show the strongest association), and in that Levey's equation had a smaller SD than the Cockcroft-Gault formula, which overestimates the true GFR at high values of serum creatinine and underestimates GFR at low values of serum creatinine [31]. However, it must be stressed that Levey's equation, to our

knowledge, has not been tested in individuals without clinically evident renal disease.

Our study supports the hypothesis that renal function itself is implicated in the association with cardiovascular mortality. Firstly, despite their different constructs, all three estimates of renal function were consistently associated with mortality. Secondly, the associations between estimates of renal function and mortality were stronger for cardiovascular than for all-cause mortality. Taken together, these findings argue against the idea that our results simply reflect poor health at baseline, in which case one might expect associations with all-cause and cardiovascular mortality of similar strength, or an association of mortality with Levey's equation (which incorporates serum albumin, a known marker of poor health) but not with the other renal function estimates.

One would anticipate that the association between renal function and cardiovascular mortality would be explained, at least in part, by other risk factors and indicators, such as hypertension and endothelial dysfunction. Individually, all these variables have been identified not only as components of the atherothrombotic process [8], but also as associated with impaired renal function [4]. Yet, in our study, the association between estimates of renal function and mortality remained after adjustment for these risk factors and indicators (compare Tables 2 and 3). The explanation for these findings is not clear. First, we cannot entirely exclude the phenomenon of residual confounding. For example, insufficient accuracy of blood pressure measurements may result in an underestimation of the confounding role of blood pressure in explaining the link between impaired renal function and mortality. On the other hand, the fact that blood pressure was related to mortality (Table 1) illustrates that the accuracy of measurement was sufficient to allow this (expected) relationship to appear. An additional argument against residual confounding is the finding that the point estimates of the associations between renal function and mortality were very similar before and after various adjustments (Tables 2 and 3). Second, we cannot exclude that some of the variables in our study insufficiently reflect the processes they are intended to measure. For example, we used plasma levels of von Willebrand factor and soluble vascular cell adhesion molecule-1 as estimates of endothelial dysfunction, but this is insufficient to fully describe the complexity of alterations in the function of the vascular endothelium. Finally, the association between renal function and mortality may reflect an unmeasured risk factor induced by impaired renal function, which then causes cardiovascular disease, or be an outcome of an underlying pathological process that affects both GFR and risk of cardiovascular mortality (for example, atherosclerosis) [32]. These possibilities require further study.

Two final limitations of our data should be kept in mind. First, we studied a relatively healthy Caucasian

population, and it remains to be established whether our results can be generalized to other racial groups or high-risk populations. Second, although our data suggest a linear inverse relationship between GFR and mortality, the population was too small to investigate whether there is a threshold of GFR below which the risk of mortality suddenly increases.

In conclusion, we have shown that mild to moderate loss of renal function is strongly associated with increased risk of cardiovascular mortality. The mechanism behind this association is unclear but does not appear to involve common risk factors such as hypertension, diabetes or hyperhomocysteinemia. Estimation of GFR, by relatively simple methods, may therefore be a valuable tool for cardiovascular risk assessment over and above that provided by conventional risk factors. Our results were obtained in a general middle-aged to elderly population, and may therefore have broad applicability.

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## REFERENCES

1. FOLEY RN, PARFREY PS, SARNAK MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 9:S16–23, 1998
2. CULLETON BF, LARSON MG, WILSON PW, et al: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56:2214–2219, 1999
3. GARG AX, CLARK FC, HAYNES RB, et al: Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 61:1486–1494, 2002
4. LEVEY AS, BETO JA, CORONADO BE, et al: Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 32:853–906, 1998
5. PERRONE RD, MADIAS NE, LEVEY AS: Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem* 38:1933–1953, 1992
6. COCKROFT DW, GAULT MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
7. LEVEY AS, BOSCH JP, LEWIS JB, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130:461–470, 1999
8. JAGER A, STEHOUWER CDA: Early detection of diabetic and nondiabetic subjects with increased cardiovascular risk: New risk indicators. *Heart Metab* 5:4–14, 1999
9. BEKS PJ, MACKAAY AJ, DE NEELING JN, et al: Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: The Hoorn study. *Diabetologia* 38:86–96, 1995
10. JAGER A, KOSTENSE PJ, NIJPELS G, et al: Microalbuminuria is strongly associated with NIDDM and hypertension, but not with the insulin resistance syndrome: The Hoorn Study. *Diabetologia* 41:694–700, 1998
11. ISLES CG, PATERSON JR: Serum creatinine and urea: Make the most of these simple test. *Br J Hosp Med* 55:513–516, 1996
12. DUBOIS D, DUBOIS EF: A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 17: 863–871, 1916
13. HOOGEVEEN EK, KOSTENSE PJ, JAGER A, et al: Serum homocysteine level and protein intake are related to risk of microalbuminuria: The Hoorn Study. *Kidney Int* 54:203–209, 1998
14. PRINEAS RJ, CROW RS, BLACKBURN H. *The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification*. Boston, Littlejohn, 1982
15. ANONYMOUS: The sixth report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. *Arch Intern Med* 157:2413–2446, 1997
16. WORLD HEALTH ORGANIZATION: *International Classification of Diseases* (9th ed, vol 1, 2). Geneva, WHO, 1977
17. FERRANNINI E, HAFNER SM, MITCHELL BD, et al: Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 34:416–422, 1991
18. MOLARIUS A, SEIDELL JC, SANS S, et al: Varying sensitivity of waist action levels to identify subjects with overweight or obesity in 19 populations of the WHO MONICA Project. *J Clin Epidemiol* 52: 1213–1224, 1999
19. NATIONAL CHOLESTEROL EDUCATION PROGRAM: Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 89:1333–1445, 1994
20. JAGER A, VAN HINSBERGH VW, KOSTENSE PJ, et al: von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects: The Hoorn Study. *Arterioscler Thromb Vasc Biol* 19:3071–3078, 1999
21. FLACK JM, NEATON JD, DANIELS B, et al: Ethnicity and renal disease: lessons from the Multiple Risk Factor Intervention Trial and the Treatment of Mild Hypertension Study. *Am J Kidney Dis* 21: 31–40, 1993
22. JUNGERS P, MASSY ZA, KHOA TN, et al: Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: A prospective study. *Nephrol Dial Transplant* 12:2597–2602, 1997
23. FRIEDMAN PJ: Serum creatinine: An independent predictor of survival after stroke. *J Intern Med* 229:175–179, 1991
24. MATTS JP, KARNIGIS JN, CAMPOS CT, et al: Serum creatinine as an independent predictor of coronary heart disease mortality in normotensive survivors of myocardial infarction. *J Fam Pract* 36: 497–503, 1993
25. MANN JF, GERSTEIN HC, POGUE J, et al: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134:629–636, 2001
26. RUILOPE LM, SALVETTI A, JAMERSON K, et al: Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 12:218–225, 2001
27. SCHILLACI G, REBOLDI G, VERDECCHIA P: High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med* 161:886–891, 2001
28. SHULMAN NB, FORD CE, HALL WD, et al: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 13:180–193, 1989
29. WANNAMETHEE SG, SHAPER AG, PERRY IJ: Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke* 28:557–563, 1997
30. FRIED LP, KRONMAL RA, NEWMAN AB, et al: Risk factors for 5-year mortality in older adults: The Cardiovascular Health Study. *JAMA* 279:585–592, 1998
31. KEMPERMAN AW, KREDIET RT, ARISZ L: Formula-derived prediction of the glomerular filtration rate from plasma creatinine concentration. *Nephron* 91:547–548, 2002
32. SARNAK MJ, LEVEY AS: Cardiovascular disease and chronic renal disease: A new paradigm. *Am J Kidney Dis* 35(Suppl):S117–S131, 2000